PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Benefits of probiotics in preterm neonates in low and medium income countries - a systematic review of randomised controlled trials
AUTHORS	DESHPANDE, GIRISH; Jape, Gayatri; Rao, Shripada; Patole, Sanjay

VERSION 1 – REVIEW

REVIEWER	Wanderley Marques Bernardo Medical School - University of São Paulo – Brasil No Competing Interest
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	Good work !!!

REVIEWER	Dr Victoria Allgar University of York, England
REVIEW RETURNED	31-Jul-2017

GENERAL COMMENTS	The is a well written paper. From a statistical perspective my only comment is that where the analysis indicates significant heterogeneity a random effects model should be chosen, otherwise a fixed effects model can be applied. Statistical heterogeneity can be assessed using the Cochran's Q test, which showed significant findings for the effect of probiotics on time to full feeds.

REVIEWER	Prof Aggrey Wasunna School of Medicine University of Nairobi Kenya No Competing Interest
REVIEW RETURNED	09-Aug-2017

GENERAL COMMENTS	This is a well performed systematic review and the conclusion is carefully worded to reflect the findings

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Bernardo):
Comment: Good work
Response: Thank you

Reviewer 2 (Allgar):
Comment: This is a well written paper. From a statistical perspective my only comment is that where the analysis indicates significant heterogeneity a random effects model should be chosen, otherwise a fixed effects model can be applied. Statistical heterogeneity can be assessed using the Cochran's Q test, which showed significant findings for the effect of probiotics on time to full feeds.

Response:
We agree with the reviewer's observation that on fixed effect model meta-analysis for the outcome of time to full feeds, there was significant statistical heterogeneity with the Cochran's Q, a statistic based on the $\chi 2$ test ($p<0.00001$).
Until recently, the most popular was Cochran's Q, a statistic. However, given its various limitations, in addition to the $\chi 2$ test, the Cochrane guidelines recommend quantifying the degree of statistical heterogeneity using the I2 statistic
$I2 = \{(Q-df)/Q\} X 100\%$
(where Q is the chi-squared statistic and df is its degrees of freedom). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (http://handbook-5-1.cochrane.org/)

On our meta-analysis for the outcome of time to reach full enteral feeds, the I2 squared statistic also showed a very high degree of heterogeneity (90%).

Hence, we cross checked the results using random effects model and presented both the results for the sake of transparency. It was reassuring to note that even on random effects model, the results continued to show beneficial effects of probiotics in improving the time to reach full feeds. We have now given the forest plot of random effects model instead of the fixed effect model for this outcome (figure 5).

Reviewer 3 (Wasunna):
Comment: This is a well performed systematic review and the conclusion is carefully worded to reflect the findings

Response: Thanks for the feedback

VERSION 2 – REVIEW

REVIEWER	Dr Victoria Allgar University of York
REVIEW RETURNED	20-Sep-2017

GENERAL COMMENTS	This is clearly written paper. My only comment on the statistical analysis is that in the methods section it states that Random-effects model (REM) analysis was conducted, however fixed effects models were used where there was no significant heterogeneity. This should be stated in the methods section regarding the decisions to choose random or fixed effects models.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 comments:
My only comment on the statistical analysis is that in the methods section it states that Random-effects model (REM) analysis was conducted, however fixed effects models were used where there was no significant heterogeneity. This should be stated in the methods section regarding the decisions to choose random or fixed effects models.

Response: The lines under /Methods' have been edited as follows: Fixed-effects model (FEM) (Mantel–Haenszel method) was used. Random-effects model (REM) analysis was conducted to recheck the results if there was significant heterogeneity on FEM.